

Two cases of acute toluene intoxication

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Abstract

Two patients exposed to high concentrations of toluene in air (> 7000 mg/m³) were found at the bottom of a small swimming pool under construction. Their symptoms were stupefaction, paresis, and amnesia. Patient A had been exposed for three hours and patient B for two hours. Ninety minutes after the exposure, the toluene blood concentration in patient A was 4.1 mg/l and in patient B 2.2 mg/l. Urinary ortho-cresol secretion was shown to be a good index of exposure to toluene. After high level exposure, urinary meta-cresol excretion may also be used to monitor toluene exposure.

Toluene is a widely used solvent and occupational exposure is common. A particular type of intoxication is caused by glue sniffing which, in some industrialised countries, has become a social problem. It is popular because toluene induces pleasant sensations, relaxation, and tranquility. Exposure to high concentrations resulting in severe toluene intoxication, except during sniffing, is observed infrequently and clinical and toxicological observations in cases of serious intoxications are scarce.

We describe two patients with severe, acute toluene intoxication. Special attention is paid to the metabolism of toluene in man and to the choice of reference parameters to monitor intoxication.

Case histories

Two men (aged 43 and 34) had tiled a small swimming pool (6.0 m long, 0.90 m broad, and 2.5 m deep) to be used for exercise programmes in a rehabilitation clinic. Subsequently they had made the joints of cement between the tiles resistant to bleaching solutions with a special glue. The next day they removed the excess of glue from the tiles with toluene. Patient A started work at 0900 and patient B at 1000. By coincidence, at 1215 both patients were found by their colleagues lying at the bottom of the pool.

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The symptoms observed when they were found were stupefaction, paresis, and amnesia. They were lifted from the bottom of the pool and subsequently admitted to the University Hospital, Utrecht.

Both patients had previously been in good health. Physical examination was carried out one hour after they were found.

PATIENT A

Patient A had mucosal irritation of the eyes and slurred speech. He was stuporose and unable to walk or sit. Blood pressure was 140/70 mm Hg and pulse 56 BPM. Auscultation of heart and lungs showed no abnormalities; on examination the abdomen was normal.

There were no haematological disorders. The concentration of serum creatinine was 78 μ mol/l, urea 7.1 mmol/l, sodium 141 mmol/l, potassium 4.5 mmol/l, chloride 105 mmol/l, and bicarbonate 24 mmol/l. Total bilirubin concentration, alkaline phosphatase activity, serum aspartate aminotransferase activity, and serum alanine aminotransferase activity were within the normal range. Blood gases, while room air was breathed, were PaO₂ 71 mm Hg and PaCO₂ 41.9 mm Hg. Arterial pH was 7.39. The anion gap was 16.5 mmol/l (normal < 13 mmol/l). Blood toluene concentration was 4.1 mg/l; the table shows the urinary ortho-, meta-, and para-cresol and phenol concentrations after exposure. The electrocardiogram showed a sinus bradycardia. The chest x ray film was normal.

The amnesia lasted from about 1015 until 1330. About four hours after being found, patient A experienced increasing pain in his right arm. Physical examination showed no fractures, contusions, or haematomas and the pain was probably caused by distortion of the elbow when he was lifted out from

Urinary excretion of some metabolites of toluene (mg/g creatinine)

	o-Cresol	m-Cresol	p-Cresol	phenol
<i>Patient A</i>				
9-6 h	10.7	2.62	52	3.57
6-18 h	6.2	2.43	57	4.53
18-24 h	12.4	1.77	38	3.68
<i>Patient B</i>				
0-6 h	6.9	2.29	50	2.29
6-18 h	3.0	1.34	35	2.04
18-24 h	10.5	2.57	56	3.57

the pool. Presumably, the pain was not felt until after several hours because of the analgesic effect of the toluene. He was discharged from the hospital five hours after being found and his only complaint then was pain in his right elbow.

PATIENT B

Patient B had mucosal irritation of the eyes, was drowsy, and was just able to walk. He had normal speech and complained of headache. Blood pressure was 120/80 mm Hg, pulse rate 116 BPM. Auscultation of the heart showed a systolic murmur in the left parasternal, third intercostal space (grade I/VI). Auscultation of the lungs showed no abnormalities. On examination of the abdomen the liver was just palpable.

The haemoglobin concentration, platelets, and white cell counts were within the normal range. The concentration of serum creatinine was 76 $\mu\text{mol/l}$, urea 4.4 mmol/l, potassium 4.5 mmol/l, sodium 140 mmol/l, chloride 106 mmol/l, and bicarbonate 24.2 mmol/l. Total bilirubin concentration, alkaline phosphatase activity, serum aspartate aminotransferase activity, and serum alanine aminotransferase activity were within normal ranges. Blood gases, while room air was breathed, were: PaO_2 85 mm Hg, PaCO_2 39 mm Hg. The arterial pH was 7.40. The anion gap was 14.3 mmol/l. The blood toluene concentration was 2.2 mg/l; the table shows the urinary o-, m-, and p-cresol, and phenol concentrations. The electrocardiogram showed a sinus tachycardia. The chest x ray film was normal.

The duration of amnesia in this patient was from about 1015 to 1245. He recovered within two hours and was discharged from the hospital in good health five hours after being found.

Both patients were investigated 24 hours and one week after the exposure. During this period no haematological disorders or renal and hepatic involvement were observed. In the first week after exposure the first patient sometimes had periods of slight pain in his right elbow but thereafter, he was free of complaints.

Materials and methods

The toluene concentration in blood was determined by capillary gas chromatography with flame ionisation detection. After the blood sample had been collected, the blood was put into a special head space vial of glass with a content of about 45 ml, closed with a rubber membrane with a Teflon lining, and stored at 4°C. The vial may be stored for several days without loss of toluene. A gas tight syringe of 1000 μl (Precision Sampling type Pressure Lok) was used for injection of head space air. From the head space air, an aliquot of 200 μl was used for gas chromatographic analysis on a Carb Erba 4130 GC (Carb Erba

Strumentazione, Milan, Italy). Separation took place on a 26 m glass capillary column WCOT CP Sil 5 CB (Chrompack, Middelburg, NL) with an internal diameter of 0.34 mm and a film thickness of 1.3 μm . Hydrogen was used as carrier gas and was set at a pressure of 1.8 bar. Column temperature was programmed from 40°C to 160°C at a rate of 20°C/min. For quantifying the results, an external calibration curve was made by using head space analysis of calibration samples of 0.2 and 10 μl of toluene dissolved in 1000 ml H_2O . This mixture was vigorously shaken for 15 minutes. Next, the samples and the calibration samples were incubated at room temperature for two hours. A sample without toluene showed no detectable toluene concentration. The detection limit was < 10–50 $\mu\text{g/l}$. Subsequently, the toluene concentration of the samples were determined and converted by using the calibration curve.

O-, m-, and p-cresol and phenol were determined in urine by gas chromatography with flame ionisation detection. The cresols and phenol were extracted from urine with liquid-liquid extraction after acidic hydrolysis. To 5 ml of urine, 1 ml of internal standard solution (800 mg 3,4-dimethylphenol per litre of water) and 1 ml of concentrated hydrochloric acid were added. The urine sample was hydrolysed by heating the mixture in a water bath of 70°C for two hours. After cooling down to room temperature, 1 ml of isopropyl ether was added. The mixture was vigorously shaken for 15 minutes and subsequently centrifuged. The supernatant isopropyl ether was transferred into a sample vial and 2 μl was used for a gas chromatographic analysis. Separation was on a borosilicate glass column (6 ft long, 2 mm internal diameter) packed with 80/100 mesh Carbowack C coated with 0.1% SP-1000 (Supelco). Helium (30 ml/min) was used as a carrier gas. Typical retention times were of phenol 1.52 minutes, of o- 3.92, of m- 4.54, and of p-cresol 4.88, and of 3,4 dimethylphenol 17.43.

Discussion

The history in these cases was suggestive of exposure to toluene. The symptoms of stupefaction, paresis, and amnesia were compatible with severe toluene intoxication and caused by severe depression of the central nervous system.

Solid evidence for toluene intoxication was provided by the blood toluene concentration. The blood toluene concentration two hours after exposure was in patient A 4.1 mg/l and in patient B 2.2 mg/l. The blood toluene concentration is below the detection limits in unexposed individuals. Carlsson found, 90 minutes after the end of the exposure to toluene, a blood toluene concentration of 18–30% of the concentration at the end of the exposure.¹ After a period of 90 minutes, Veulemans found a toluene concentration around 30% of the concentration at the end of

the exposure; after 120 minutes, the concentration was $25^{0.2}$. The decrease of toluene concentration is most pronounced within the first few minutes, further decline occurs more gradually.^{2,3} From these data it may be concluded that the blood toluene concentration in both patients was much higher at the end of the exposure than that determined subsequently. Toluene blood concentrations in post-mortem specimens of fatal cases have varied from 10 to 33 mg/l.^{4,5}

Hepatic and renal involvement was not noticed. The anion gap was slightly increased (in patient A 16.5 mmol/l and in patient B 14.3 mmol/l) either from distal tubular acidosis or increased concentration of the metabolites of toluene. Fischman and Oster and Patel and Benjamin described distal tubular acidosis in patients who were exposed chronically to high concentrations of toluene.^{6,7} Fischman and Oster suggested that an increased anion gap could also be caused by an increased concentration of the metabolites of toluene such as benzoic acid or hippuric acid. Since the present patients were not chronically exposed to high toluene concentrations the anion gap seems to have been caused by an increase in the concentration of metabolites of toluene.

The high toluene concentration in the swimming pool provided evidence that both patients were seriously exposed to toluene. Three hours after the patients were rescued the toluene concentration was $> 7000 \text{ mg/m}^3$ ($= 1842 \text{ ppm}$) at the edge of the pool. A more precise calculation could not be made by the fire brigade because the concentration was determined by Dräger tubes. Since toluene is heavier than air it had probably sunk to the bottom of the pool where the concentration was presumably even higher.

The acute effects observed in man of a single, short term exposure to a toluene concentration of 1500 mg/m^3 are headache, dizziness, irritation of the throat and eyes, lachrimation, skin paraesthesia, incoordination, and mental confusion. With exposure to 3000 mg/m^3 the symptoms can be nausea, confusion, ataxia, amnesia, serious reduction in reaction time, and lack of self control. The effects after exposure to 15000 mg/m^3 cause rapid impairment in reaction time and coordination. Exposure of one hour or more to this concentration may lead to narcosis and probably to death.⁸

Toluene is readily absorbed by inhalation and ingestion and rapidly metabolised by two oxidative routes. The major route is oxidation of the aliphatic chain. Approximately 80% of an absorbed dose is metabolised by this route with the formation of benzoic acid which is further conjugated either with glycine to hippuric acid, or with glucuronic acid to benzoyl glucuronic acid. The minor route is oxidation of the aromatic ring which potentially results in

formation of o-, m-, and p-cresol. The cresols are excreted in urine as their corresponding glucuronide and sulphate conjugates.⁹

Since several food products contain benzoic acid, urinary hippuric acid excretion is related to intake of benzoic acid via the food. This causes a considerable, intraindividual variation. In a group of 39 unexposed individuals urinary hippuric acid excretion ranged between 0.086 and 2.340 g/g creatinine (mean 0.739 g/g creatinine).¹⁰ On a group urinary hippuric acid excretion may be used to monitor exposure to toluene but on an individual basis it is an unambiguous index only after exposure to toluene concentrations above 3040 mg/m^3 ($= 800 \text{ ppm}$).¹¹ For similar reasons the excretion of benzoyl glucuronic acid is not a suitable index of toluene exposure.

Para-cresol is a normal constituent of urine of individuals not exposed to toluene. In 85 male human volunteers we determined the urinary para-cresol excretion and the results are shown in fig 1. On the basis of these results, we calculated the reference values to be 3.3–63 mg/g creatinine. Obviously p-cresol is not a suitable index of exposure to toluene either. For the same reason, urinary phenol excretion, which was determined in the same group of male healthy volunteers, is not an adequate indicator of exposure to benzene (fig 2); reference values for urinary phenol excretion were to be 0.8–16 mg/g creatinine.

In most published analytical procedures for determining cresols in urine, m- and p-cresol are not separated. Our analytical procedure, however, was able to separate all three cresols. Therefore the excretion of o- and m-cresol, which are not normal constituents of the urine,¹² could be monitored as well. In the rat metabolites of toluene included o- and p-cresol but not m-cresol.¹³ In man it has been assumed that only o- and p-cresol are formed after exposure to toluene.^{14,15} A linear relation between exposure to toluene and urinary o-cresol excretion

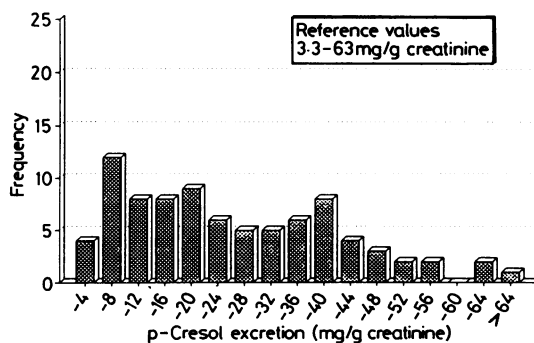


Figure 1 Frequency distribution of urinary p-cresol excretion in 85 male volunteers. Figures on concentration axis indicate upper limits of respective classes. Reference values were determined by a non-parametric method.

